5 (Twice-Amended). A hybrid protein in accordance with claim 1, wherein sequence (a) is joined, either directly or via a linker, to the carboxy terminus of sequence (b).

Please rewrite claim 14 in once-amended form as follows:

14 (Once-Amended). A hybrid protein in accordance with claim 1, wherein one or more [covalent] non-native interchain disulfide bonds between cysteine residues in the two subunits (b) are added.

Claim 6 (amended), line 4, delete "a sequence corresponding to".

REMARKS

The Office Action and the cited and applied references have been carefully studied. No claims are allowed. Claims 7-13 are withdrawn at this stage as being directed to a non-elected species. It is understood, however, that claims 7-13 will be examined later if the generic claim is found to be patentable. Claims 1-14 and 19 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claims 1-6, 14 and 19 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is obviated by the amendment to claims 1, 4-6, and 14.

Claims 1, 2, 3, 5, 14 and 19 have been rejected under 35 U.S.C 102(b) as being anticipated by Johnson et al., Biol. Reprod. 52:68-73 (1995), reference AC cited by applicants. The examiner indicates that Johnson discloses a hybrid protein

comprising βhCG fused to CH_{1-3} of mouse IgG. The examiner states the recombinant protein formed "multimeric forms of fusion protein" (abstract); and that based upon the disclosure of the composition of the protein, such would have been expected to be dimers due to disulfide bond formation between hinge regions of IgG chains. It is said that the protein was administered to rams, and thus meets the limitation of having been in the form of a pharmaceutical composition. The examiner further indicates that this rejection was necessitated by the amendment of claim 1 to include in part (a) antibody chains and states that the ability of the hCG portion of the molecule to form heterodimers is inherent to the fusion proteins of Johnson. It is noted that although claim 1 requires that sequences (b) "in each of said two coexpressed sequences are *capable* of aggregating to form a dimer complex", the claim is said to fail to specify with what they are capable of dimerizing, nor that the protein occurs as a dimer *because* of the dimerization of "sequences (b)". Thus, it is the examiner's position that the Ig constant regions as disclosed by Johnson meets the limitations of the claims. This rejection is respectfully traversed.

In Johnson's hybrid protein, dimerization occurs due to disulfide bond formation between hinge regions of IgG chains. Claim 1 is amended to clearly recite that it is sequence (b) of one coexpressed sequence that aggregates with sequence (b) of the other coexpressed sequence to form a dimer complex. Accordingly, the presently claimed hybrid protein is not dimerized by antibody chains of sequence (a) but rather by the hormone subunits of

sequence (b). Furthermore, Johnson's hybrid protein does not form a heterodimer as recited by the present claims. Therefore, the hybrid protein disclosed by Johnson cannot anticipate the presently claimed invention.

Reconsideration and withdrawal of this rejection are therefore respectfully requested.

Claims 1-5, 14 and 19 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Boime, U.S. Patent number 5,705,478, for reasons cited in the previous Office Action, mailed May 22, 1998, at pages 4-5. The examiner indicates that applicants' arguments submitted October 19, 1998, paper number 9, have been fully considered but are not deemed persuasive.

The examiner states that applicants argue that the conformation of the linker moiety/fused protein of Boime's fusion proteins when in a dimeric complex "would be quite different from its conformation in the "pseudodimeric" single-chain glycoprotein hormone as intended by Boime, and that the change in conformation would impair the biological function of the "linker moiety/fused protein". This argument has been fully considered but is not deemed to be persuasive by the examiner because, according to the examiner:

(A) While this *might* be true, it would not necessarily be true, and would be dependent upon the particular "fused protein" as well as the particular "linker moiety". Proteins are not rigid, linear strings of amino acids as would be suggested by applicants' alignments in the traversal. Many "ligands" are globular proteins, which would not necessarily be adversely affected by the change in conformation between a "pseudodimer"

and the dimeric conformation. For example, IL-3, IL-4, GM-CSF and M-CSF are all compact, globular proteins. Therefore, and in view of the breadth of the claims, the examiner maintains that there is no reason to expect the loss of activity urged by applicants.

(B) Applicants appear to be interpreting that the "linker moiety/fused protein" of Boime is the only portion of Boime's fusion that would meet the structural limitation of part (a) of claim 1. The examiner asserts that this is incorrect. As part (a) of claim 1 includes the generic "a ligand", and as glycoprotein hormones are most assuredly ligands, it is held that one of the glycoprotein hormone subunits of Boime's fusion protein would also meet the structural limitations of part (a) of claim 1.

(C) Applicants argue that, presumably *if* the "linker moiety/fused protein" in the pseudoheterodimer of Boime was not biologically active when the protein was in the dimeric form, that such would not meet the claim limitations. This argument has been fully considered but is not deemed persuasive by the examiner because it is not established that the "middle" protein would not be functional in such a dimeric configuration, because the claim does not require such activity, and because as stated in (B) above, the "middle" portion of Boime's fusion protein is not the only portion that would meet the requirement of being a "ligand".

Finally, applicants argue that there would be no way to "predetermine the ratio of psueodoheterodimer, dimers and higher

order complexes" formed by Boime's protein. This argument has been fully considered but is not deemed persuasive by the examiner because there is no such limitation in the rejected claims. It is the examiner's position that numerous species encompassed by the claims would similarly be capable of forming higher-order structures.

While applicants do not agree with the examiner's reasons for finding applicant's arguments unpersuasive, applicants believe that these issues are moot in view of applicants' amendment to claim 1 reciting that the chain from a heteromeric receptor is not from a gonadotropin receptor. The present specification discloses a number of examples of sequence (a), of which a gonadotropin receptor is merely a single example. Applicants are entitled to exclude this example of a gonadotropin receptor from the list of sequence (a) recited in Markush format. Therefore, as sequence (a) cannot be a gonadotropin receptor, it is clear that the dimers that may inherently form from Boime's single chain compounds such as βFSH-α cannot make obvious the presently claimed invention. Note that the extracellular domain of a gonadotropin receptor as recited for sequence (a) in claim 1 does not read on the variants disclosed by Boime.

Reconsideration and withdrawal of this rejection are therefore respectfully requested.

Claims 1-5, 14 and 19 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Capon et al., U.S. Patent 5,116,964, in view of Fiddes et al., references BR and BS, cited by applicants (Nature 281:351-356, 1979 and 286:684, 1980).

The examiner states that Capon teaches hybrid immunoglobulin molecules, wherein a portion of an antibody is fused via recombinant DNA technology to a heterologous protein. At col. 4, line 38, Capon is said to state that the molecules "serve to prolong the *in vivo* plasma half-life of the ligand binding partner, such as immunoglobulin domains or plasma proteins, and facilitate its purification by protein A. At column 4, beginning at line 57, Capon is also said to state that the molecules are "for directing ligand binding partners such as toxins, cell surface partners, enzymes, nutrient substances, growth factors, **hormones**, or effector molecules...", "...to cells bearing ligands for the ligand binding partners, and for use in facilitating purification of the ligand binding partners." (emphasis added by the examiner). At column 5, the examiner indicates that Capon teaches the fusion of different binding partners onto more than one chain of the immunoglobulin, to produce a multi-chain polypeptide with multiple binding functions. Therapeutic and diagnostic compositions comprising the Ig fusion proteins are said to be envisioned (column 5, line 55). Fusion of the ligand binding partner to the Ig sequence via either the amino or carboxyl termini are also said to be envisioned, see col. 10, lines 13-15 and claim 1. Although the examiner asserts that Capon discloses both the concepts of Ig fusions comprising hormones as the "ligand binding partner" and Ig fusions comprising two or more different ligand binding partners, the examiner concedes that Capon does not teach or suggest specifically Ig fusions comprising one or more subunits

of a heterodimeric proteinaceous hormone.

Fiddes is held by the examiner to teach cDNAs encoding hCGα (reference BR) and hCGβ (reference BS). Fiddes also is said to teach that "Detection of HCG by radioimmunoassay is diagnostic of pregnancy or the presence of a tumor" (reference BR, first paragraph). The examiner takes the position that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to substitute the hCG sequences taught by Fiddes either for hCGα or hCGβ, in the constructs of Capon to produce hCG:Ig fusion proteins. The examiner asserts that one of ordinary skill in the art would have been motivated to do so to attain the known and expected advantages of such as discloed by Capon, including ease of purification via protein A, and expected increased serum half life. The examiner also asserts that it would further be obvious to formulate a pharmaceutical composition comprising such to, for example, be used for the production of antibodies useful in the radioimmunoassays disclosed by Fiddes. As was stated in the new grounds of rejection under 35 U.S.C. §102(b) above, the examiner indicates that this rejection was necessitated by the amendment of claim 1 to include in part (a) antibody chains. The ability of the hCG portion of the molecule to form heterodimers is held to be inherent to the fusion proteins and obvious over Capon in view of Fiddes by the examiner. It is noted that although claim 1 requires that sequences (b) "in each of said two coexpressed sequences are *capable* of aggregating to form a dimer complex", the claim fails to specify with what they are capable of dimerizing, nor that the protein occurs as a dimer *because* of the

dimerization of "sequences (b)". Thus, the examiner maintains dimerization via the Ig constant regions as disclosed by Capon meets the limitations of the claims. This rejection is respectfully traversed.

Claim 1 is now amended to positively recite that dimerization occurs through aggregation of sequences (b). Furthermore, Capon discloses at column 5, lines 35-55:

> In a preferred embodiment in which the stable plasma protein is an immunoglobulin chain the ligand binding partner will be substituted into at least one chain and ordinarily for the variable region of the immunoglobulin or suitable fragment thereof. However, it will be understood that this invention also comprises those fusions where the same or different ligand binding partners are substituted into more than one chain of the immunoglobulin. If the ligand binding partners are different, then the final assembled multichain polypeptide is capable of crosslinking ligands in a fashion that may not be possible with multifunctional antibodies having native variable regions.
>
> A particular multichain fusion of this sort is one in which the variable region of one immunoglobulin chain has been substituted by the ligand binding region of a first receptor such as CD4 while the variable region of another immunoglobulin chain has been substituted by a binding functionality of the LHR, both immunoglobulin chains being associated with one another in substantially normal fashion.

It is clear from Capon that the variable region of the immunoglobulin chain, which is not critical to the plasma stability property of immunoglobulins as conferred by the constant domain, is substituted by a ligand binding partner. Accordingly, the polypeptide of Capon does not have a sequence

(a) which is an antibody light or heavy chain. Instead, Capon's polypeptide is a hybrid polypeptide which lacks the variable region of an immunoglubulin chain and cannot be considered to be an antibody light or heavy chain. The Fiddes references do not add to Capon's disclosure and cannot satisfy its deficiencies as noted above, and the combination of applied references therefore cannot make obvious the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

The examiner indicated that claim 6 would be allowable if amended to overcome the above rejections under 35 U.S.C. §112. Accordingly, Claim 6, as amended, is now allowable.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration, entry of the amendment, and early allowance are earnestly urged.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By: _____
Allen C. Yun
Registration No. 37,971

ACY:pr
Facsimile: (202) 737-3528
Telephone: (202) 628-5197

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